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Minor structural brain changes in young drug abusers

A magnetic resonance study

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Twenty-three drug abusers and seventeen controls underwent clinical neurological examinations and magnetic resonance imaging (MRI) of the brain. The drug abuse encompassed cannabis, inhalants, opiates, psychedelics, amphetamines, and cocaine but not necessarily all drugs in all persons. The drug abuse was always combined with heavy alcohol consumption. One drug abuser had abnormal neurological findings which consisted of lower limb ataxia and 3 others had mild imbalance. MRI examinations did not show differences in width of the third, fourth or lateral ventricles nor the diameter of the cerebral aqueduct but the drug abusers had significantly smaller vermes cerebelli compared to controls. White matter changes also occurred more often in the drug abuser group. These findings are not consistent with known side-effects of the narcotic drugs but more probably a result of very high alcohol consumptions in parallel with drug abuse. Alcohol is clearly a much more potent brain toxic agent than are the most commonly abused narcotic drugs.

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Repeated intake of cannabis, psychedelics, opiates, amphetamines or cocaine may lead to severe mental disturbances and psychiatric symptoms which have been fairly well described. The neurological complications in drug abuse are closely related to the neurotoxical properties of the substrate abused. Opiates may cause acute life-threatening respiratory inhibition but long-term use of pharmaceutical opiate products usually do not induce structural brain lesions. Amphetamine and cocaine are potent CNS sympathomimetic drugs, sometimes with neurological as well as non-neurological complications. Both drugs may cause intracerebral vasculitis, ischemic stroke, and cerebral hemorrhage especially in persons with preexisting malformations or saccular aneurysms (1–3). The psychedelic drugs like LSD and mescaline may induce psychiatric disturbances but they are usually without severe somatic side-effects.

In 1971 Campbell et al. (4) reported cerebral atrophy in an air ventriculography study of cannabis abusers. This observation has later not been confirmed by other investigators (5), and cannabis is regarded as relatively safe compared to other illicit drugs (6, 7).

The occidental drug abusers today very seldomly use only one type of drugs. Typically a number of narcotic drugs in combination with alcohol are consumed. This mixed abuse makes any research on brain injury in these type of abusers fairly complicated.

Magnetic resonance imaging (MRI) has become an important investigative tool giving more accurate information on intracranial structures compared to CT. In the present study the magnetic resonance images of the brain were examined regarding cerebral atrophy and white matter pathology. The width of the ventricular system and the size of the cerebellar vermis were calculated in drug abusers and related to findings in a corresponding young population without a history of drug or alcohol abuse.

Subjects and methods

MRI investigations were performed in 23 male drug abusers, aged 20 to 29 years, mean 24.4 years; and in 17 male controls aged 21 to 30 years, mean 24.0 years. The subjects above mentioned were all employed or under education except one who was in prison. The drug abusers were interviewed using the questionnaire from Diagnostic and Statistical Manual of Mental Disorder, DSM-III-R (8); using axis I and II designed for evaluation of psychiatric illnesses and personality disorders. The former and present abuse of different substances are clearly documented in the DSM-III-R axis I, illustrated in Table 1. All drug abusers had started with alcohol abuse

Table 1. Abuse diagnosis according to DSM-III-R criteria

1) Alcohol abuse and dependence	23
2) Cannabis abuse and dependence	23
3) Amphetamine abuse and dependence	17
4) Sedative, hypnotic, or anxiolytic abuse and dependence	13
5) Inhalant abuse and dependence	12
6) Hallucinogen abuse and dependence	11
7) Opioid abuse and dependence	11
8) Cocaine experience	12

around the age of 12 to 15 years. At this part of life about half of the patients had used inhalants during a short period of time. All had a history of cannabis abuse, usually starting in adolescence around the age of 15 to 18. In 21 patients the accumulated cannabis consumption ranged from 1 to 15 kg with a mean of 3–5 kg. Two patients had only limited experiences with cannabis, i.e. about 0.5 kg.

Seventeen patients had taken injections of amphetamines. Two had injected amphetamines more than 1000 times and 9 had taken several hundred injections.

Thirteen patients were classified as sedativa abusers regularily taking minor tranquillizers of the benzodiazepine group. Twelve patients had abused inhalants during some part of their lives, usually in the early teens. Only two of these patients had abused inhalants for more than one year.

Six patients had used amphetamine about 50 to 100 times. About 50% of the patients had tried cocaine but only in small amounts and usually of inferior quality.

Seventeen patients reported that they had been abusing hallucinogens. Some had been taking LSD but as many as eleven patients had eaten more than several hundred mushrooms, psilocyne semilanceata, containing considerable amounts of psilocybin.

Eleven patients had a history of past intravenous opiate abuse. The exact number of injections was not easy to obtain but was estimated to about a few hundreds.

All patients had very high mean alcohol consumption, everyone had at least been taking 10–15 kg of alcohol/year for more than 5 years, but not necessarily during the 5-year period just prior to admission. When including cannabis and alcohol each patient had a mean abuse- or experience diagnose of 5.3 drugs.

All drug abusers except one had a blood sample taken prior to the neurological examinations and these were screened for THC (tetrahydrocannabinoid, a metabolite of cannabis), benzodiazepine, opiates, amphetamine and alcohol. The one who was not tested was well-known by the examiners, and was judged to be in a stable off-drug period at the time when the present investigations took place.

The controls belonged to the ordinary staff at the psychiatric hospital. They were interviewed about drug abuse and none in this group had tried other stimulants than alcohol. The alcohol consumption among the controls was low, far below 5 kg of alcohol/year, which is the mean alcohol consumption among adult male Norwegians.

MRI investigations

The MRI examinations were performed on a Philips Gyroscan S15 operating at 1.5 Tesla. Transverse intermediately- and T2-weighted images (TR > 2100 ms, TE 29/90 ms) with 6.5 mm slice thickness, and coronal and sagittal T1-weighted images (TR 500 ms, TE 30 ms) with 5 mm slice thickness were acquired. The coronal series were performed perpendicularly to the McGregor line, midline cut through dorsum sellae. The width of the cerebral aqueduct and the 3rd and 4th ventricles were measured. In the midline sagittal cut a region of interest (ROI) was drawn around the vermis and the volume was calculated based on the surface of the ROI multiplied by the slice thickness. The volume of the lateral ventricles was calculated from the coronal cuts. The number of white matter lesions was noted.

The 40 MRI examinations and evaluations in drug abusers and controls were done in a blinded manner.

Results

Clinical investigations – The neurological examination revealed that only one patient had evident signs of brain lesion. This was a 22-year-old man who had been using alcohol for about 10 years and who had taken about 500 injections of amphetamines. He had also been through a period of inhalants abuse and had taken several hundred hallucinogenic fungi but relatively limited amounts of cannabis and opiates. He had not tried cocaine. The neurological signs consisted of discrete ataxia and imbalance. When tested in the supine position and asked to place the heel at the opposite knee and slide the heel downward over the shin a pronounced slow tremor was precipitated. Similar examinations in the rest of the patients were negative although 3 had minor difficulties when performing the Romberg test with closed eyes and on walking with closed eyes. None of these signs were detectable without the specific neurological test-battery. None of them was aware of any subclinical ataxia or imbalance.

Toxicological investigations – The blood samples revealed that 13 persons had been taken cannabis during the week prior to examination and two further had taken benzodiazepines. The serum levels of

THC and benzodiazepines were low and probably without any impact on clinical test results.

MRI results

The measurements of 5 intracerebral parameters are listed in Table 2. The size of the ventricular system did not differ between the groups. The drug abuser had larger lateral ventricles compared to the controls but this difference was not statistically significant. The size of the third ventricle differed only 2% between the groups. The mean widths of the aqueduct and the 4th ventricle both differed by less than 5% between the groups. It is worth noting that the control group had a mean width of the 4th ventricle which was larger than that of the drug abusers.

Regarding the vermis cerebelli a significant difference between the groups was found (Fig). The mean volume of the vermis was 18% larger among the controls than in the group of drug abusers ($p < 0.005$), (t-test). A separate evaluation was carried out within each group of drugs, except cannabis and alcohol, between those patients who had been abusing that particular drug and those who had not taken the drug. These intra-drug comparisons did not reveal differences between abusers and non-abusers in any particulary drug except alcohol.

White matter changes were noted (Table 3). About 17–18% of abusers and controls had small abnormal changes in the brain, thus the group did not differ in this respect. Nine drug abusers (39%) had small hyperintense foci in one or both nuclei lentiformes compared with five (29%) in the control group (no significance; n.s.). However, MRI showed a significantly higher number of cerebral cortical atrophy in the group of abusers. One of the controls (6%) was diagnosed as atrophy of the cortical hemispheres. The corresponding data for the drug abusers was 7 (30%) and within this group 4 had clinical atrophy of the ventricular system and 2 of the cerebellar cortex.

Table 2. MRI of the brain of drug abusers

Anatomical region	Drug abusers (n=23)	Controls (n=17)	Significance
Lateral ventricle (cm^3)	7.67	6.00	n.s.
SD	3.87	3.66	
Aqueduct (mm)	1.22	1.20	n.s.
3rd ventricle (mm)	4.43	4.06	n.s.
SD	1.72	1.39	
4th ventricle (mm)	10.30	10.88	n.s.
SD	1.69	1.69	
Vermis cerebelli (cm^3)	6.33	7.44	$p < 0.005$
SD	1.28	0.87	

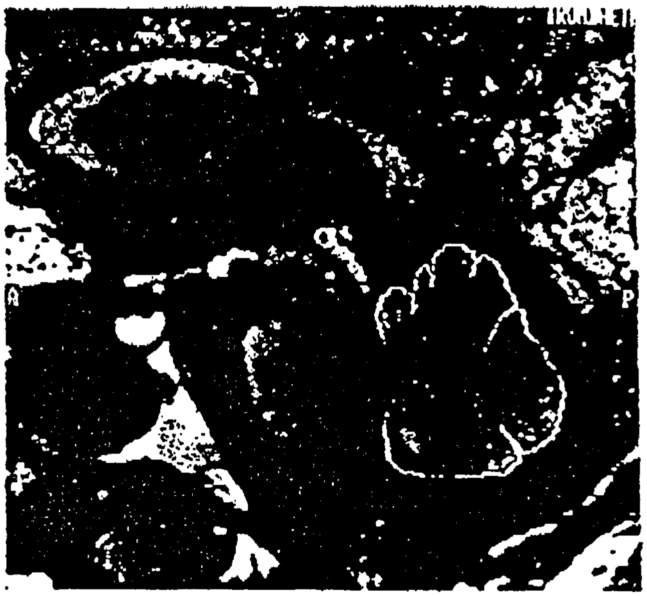

Fig. 1. Magnetic resonance, T-1 weighted midline sagittal image showing moderate cerebellar atrophy. The cerebellar vermis is marked.

Table 3. Location of cortical and white matter changes in the brain in drug abusers and normal controls

Type of MRI pathology	Drug abusers	Controls
White matter changes	4 (17%)	3 (18%)
– Frontal	1	0
– Parietal	2	2
– Occipital	2	2
Nucleus lentiformis lesions		
– Unilateral	3	2
– Bilateral	6	3
Summed	9	5
Cortical atrophy		
– Remarked in* locations:	7 (30%)	1 (6%)
– Cerebral hemispheres	4	1
– Ventricular	4	0
– Cerebellar	2	0

* 3 pts had more than one remarks.

According to Table 1, alcohol abuse and cannabis abuse occurred in all drug abusers while psychedelic mushrooms, opiates, amphetamines and cocaine were abused less frequently. Drug abusers were grouped in two parts for each of the former mentioned drugs; those with and those without experience with that particular drug. There was no difference between the two groups in any of these drugs classes.

Discussion

The documented evidence of cerebellar vermis atrophy among the abusers indicates toxic effects of one or several of the drugs abused. Cannabis was the most widely abused narcotic drug in this group in combination with high alcohol consumption. All other illicit compounds were more or less to be regarded as adjuvants, and abused if and when available, except inhalants which only had been used for a short period of time in the early teens. In this way our patients represented a typical sample of mixed abusers. They did not belong to the group of addicts in whom temporary malnutrition may add further damage to the nervous system.

According to Campbell et al. (4) cannabis could induce enlargement of the lateral ventricles and cortical atrophy, none on which was observed in the present study. Later studies by other investigators (5) regarding structural brain changes in cannabis have not been able to confirm those early observations and cannabis has been considered as a relatively harmless drug regarding brains lesions. About half of our patients had tried or abused inhalants during a part of life, usually as their first or second substance abuse but none had extensively experience with these substances. It is well known that inhalant abuse may lead to brain atrophy but this is less likely in our population since drug abusers with inhalant abuse did not differ from those without such a history. Organic cerebral lesions from inhalant abuse also seem to be related to very high and long-time consumption not comparable to the relatively brief periods among participants in the present study. This was also the case in those who had been using psychedelic mushrooms. Hallucinogenic drugs are known to be very little toxic and without major impact on structural brain changes.

Opiates have been used for medical treatment for years in high dosed without giving structural changes. However, opiates for sale on the street are often of inferior quality and may be hazardous to abuse under certain circumstances. It should be recalled that MPTP and its metabolites, toxic to the basal ganglia, and induced severe parkinsonism in a group of young addicts, were a contaminant of improper meperidine synthesis (9). This in fact always rises the question if the findings in studies in drug abusers really are results from known substances or from some which might be contaminants in this multiplicity of inferior quality products.

Brain lesions induced by drug abuse are more likely to occur in persons abusing amphetamines or cocaine. Both drugs as well as illicit drugs within the opiate group may cause cerebral vasculitis (1). There were no case histories among our patients indicating such side-effects and angiographic examinations were not performed. Amphetamines and cocaine are sympathomimetic drugs causing an excess of adrenPatients with an intracerebral vascular malformation or aneurysms are at particular risk when abusing these drugs. The white matter lesions seen in the drug abuser group were to small to indicate such pathogenesis (10).

Alcohol is the only drug abused in the drug abuser group which is known to induce cerebral atrophy, both manifesting itself as cortical atrophy, ventricular enlargement and atrophy of the cerebellum. The alcoholic cerebellar degeneration is relatively common among alcoholics usually seen as gait ataxia and caused by atrophy mainly of the anterior portions of the vermis and the anterior lobes (11, 12).

The mild ataxia seen in one of the patients was of exactly the same type as has been described in alcoholics but may also sometimes be seen after heavy inhalant abuse (13). Ataxia could be related to alcohol abstinence or other substance abstinence although this is less likely since the blood samples showed that the substance abuse during the week prior to examination had been fairly low. An abstinence tremor would probably have been most pronounced in the group of patients with clean tests since cannabis may have some beneficial effect on severe ataxia (14, 15).

There were 4 drug abusers who showed mild balance difficulties when walking on a line with closed eyes. These symptoms must be regarded as unspecific and without predicting value of neurologic disease. However, one of these abusers also showed absolute and clear ataxia of the same kind as that seen in patients with severe alcoholism (16). This same abuser also had the smallest vermis e.g. the most pronounced cerebellar atrophy, about 40% reduction compared to the mean vermis size in controls. The degree of cerebellar atrophy needed for producing clinical symptoms is not known. From the present study the patients seem to be without symptoms if the cerebellar reduction is less than 35%.

The etiology behind the cerebellar atrophy remains unsolved but several authors have claimed that the most probably cause is malnutrition (11). All young men who took part in our study were well nourished and had not been through any periods of clinical importance of impaired food intake or malabsorbtion.

Continued detailed study of the brain is needed to provide a more coherent picture of the toxic effects of illicit drugs. The present study indicates that drug abusers can develop structural brain changes early in life consisting of a mild enlargement of the lateral ventricles and atrophy of the cerebellar vermis. Young drug abusers also have a very high alcohol consumption parallel to narcotic drug abuse. Our

25 years probably due to chronic alcohol abuse. One should keep in mind that neurological deficits in drug abusers are more likely to occur from alcohol abuse than from other illicit drugs and that alcohol is widely abused also in so-called narcotic drug abusers.

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